86-341404/52 B04 TRES/ 09.05.85
TRESSENS D J P *FR 2581-543-A
09.05.85-FR-006998 (14.11.86) A61k-37/26
Insulin preparation for oral administration - by coating in multi-vesicular liposome(s), encapsulation, and gastro:resistant coating
C86-148029

B(4-B1B, 4-B2D2, 4-C2A3, 12-H5, 12-M10B, 12-M11F)

An insulin preparation active on oral administration is prepared as follows:
(i) insulin is envesiculated in multivesicular liposomes which ensure the stability of the insulin in intestinal media;
(ii) this product is then lyophilised;
(iii) the lyophilisate is put into capsules; and
(iv) the capsules are coated with a gastro-resistant coating to form the final product.

USE/ADVANTAGE

Insulin is a specific treatment for hyperglycemia, but is destroyed by proteolytic enzymes of the digestive system. The new preparation is stable and is active orally.

PREPARATION

A lipid phase is prepd. by dissolving amphiphilic phospholipids and neutral lipids in a mixture of chloroform and ether. Insulin is dissolved in aqueous maltose solution. The aqueous phase and the lipid phase are mixed and gently stirred. The mixture is sealed, air is replaced by nitrogen, and the mixt. is stirred vigorously for 12 minutes.

The resultant emulsion is added to a solution of maltose which is more concentrated than that used previously, and stirred gently under nitrogen. The mixture is heated gently to evaporate the organic solvents, leaving envesiculated material which is separated from lipid debris and other undesired materials by dialysis or centrifuging.

The product is lyophilised and placed into capsules which are then made gastro-resistant by successive coatings of a material which is not attacked by the gastric medium.

EXAMPLE

Insulin multivesicular liposomes were prepared from 0.450 mole phosphatidyl ethanolamine, 0.450 mole cholesterol, 0.100 mole phosphatidyl serine, 0.100 mole triolein in 100 litres of an equal mixture of chloroform and ether, and from a solution of 150 g. crystalline insulin in 100 litres 0.15M aqueous maltose. The more concentrated solution of maltose was 500 litres of 0.20M.

Gastro resistance was effected with successive coatings of cellulose acetophthalate.(6pp520EDDwgNo0/0).FR2581543-A

DERWENT PUBLICATIONS LTD.